Review Article

Kidney360

Modifiable Lifestyle Behaviors and CKD Progression: A Narrative Review

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Abstract

Living a healthy lifestyle is one of the safest and most cost-effective ways to improve one's quality of life and prevent and/or manage chronic disease. As such, current CKD management guidelines recommend that patients adhere to a healthy diet, perform ≥150 minutes per week of physical activity, manage their body weight, abstain from tobacco use, and limit alcohol. However, there are limited studies that investigate the relationship between these lifestyle factors and the progression of CKD among people with established CKD. In this narrative review, we examine the reported frequencies of health lifestyle behavior engagement among individuals with non–dialysis-dependent CKD and the existing literature that examines the influences of diet, physical activity, weight management, alcohol consumption, and tobacco use on the progression of CKD, as measured by decline in GFR, incident ESKD, or elevated proteinuria or albuminuria in individuals with CKD. Many of the available studies are limited by length of follow-up and small sample sizes, and meta-analyses were limited because the studies were sparse and had heterogeneous classifications of behaviors and/or referent groups and of CKD progression. Further research should be done to determine optimal methods to assess behaviors to better understand the levels at which healthy lifestyle behaviors are needed to slow CKD progression, to investigate the effect of combining multiple lifestyle behaviors on important clinical outcomes in CKD, and to develop effective techniques for behavior change. Despite the lack of evidence of efficacy from large trials on the ability of lifestyle behaviors to slow CKD progression, maintaining a healthy lifestyle remains a cornerstone of CKD management given the undisputed benefits of healthy lifestyle behaviors on cardiovascular health, BP control, and survival.

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Introduction

CKD is an epidemic, affecting more than one in ten American adults (1). Patients with CKD have a high burden of risk factors for cardiovascular disease (CVD) and experience high rates of CVD events. Maintaining a healthy lifestyle offers a crosscutting approach to reduce the risk of CVD. Lifestyle behaviors are similarly recommended across relevant guidelines, including the Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of CKD, the KDIGO 2020 Guidelines for Diabetes Management in CKD, and the American College of Cardiology/American Heart Association guidelines on the primary prevention of CVD (Table 1) (2,3). In the CKD population, lifestyle behaviors, such as diet, physical activity, weight management, alcohol consumption, and tobacco use, have mainly been studied in relation to reducing CVD events and mortality risk (4–6), and less is known about limiting CKD progression. The purpose of this narrative review is to describe the current evidence of how select lifestyle behaviors relate to CKD progression, defined as progressive decline in GFR, development of ESKD, or increase in proteinuria or albuminuria among people with established CKD without kidney failure requiring transplant or dialysis. Using PubMed, we selected observational studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses that focused on the relationship of lifestyle behaviors and CKD progression. The search terms included the following: CKD progression, end-stage renal disease, ESRD, end-stage kidney disease, ESKD, glomerular filtration rate decline, GFR decline, lifestyle factors, diet, dietary pattern, dietary acid load, potential renal acid load, sodium, potassium, protein, phosphorous, smoking, smoking cessation, marijuana, alcohol, physical activity, exercise, obesity, body mass index, and BMI. We did not include studies that investigated the effect of multiple lifestyle behaviors and, therefore, this review does not cover how lifestyle behaviors in combination relate to CKD progression. As a narrative review, we were not inclusive of all published studies assessing the relationship between lifestyle behaviors and CKD progression, which limits our ability to assess all published results, but we have focused on including high-quality studies and limiting inclusion of studies that reported very similar results.

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Table 1. Lifestyle behavior recommendations across clinical practice guidelines

Lifestyle Behavior (Definition/ Measures)	Guideline Recommendations		
	General CKD Management (89)	CKD Management with Diabetes (17)	Cardiovascular Disease Primary Prevention for General Population (90)
Diet (defined by components consumed, including macronutrients and micronutrients)	Individuals should receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated	Individuals should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages	Individuals should consume a healthy diet that emphasizes the intake of vegetables, fruits, nuts, whole grains, and fish; eliminate trans fats and minimize the intake of processed meats, refined carbohydrates, and sweetened beverages; replace saturated fat with monounsaturated and polyunsaturated fats, and reduce dietary cholesterol and sodium
Physical activity (bodily movement produced by skeletal muscle that requires energy expenditure)	Individuals should be encouraged to undertake physical activity compatible with cardiovascular health and tolerance (aiming for at least 30 minutes five times per week)	Individuals should undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance	Individuals should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity; for those unable to reach this minimum, engaging in at least some moderate-to-vigorous activity can still be beneficial
Healthy weight management (BMI is the predominant index to establish body habitus in clinical practice)	Individuals should be encouraged to achieve a healthy weight (BMI 20–25 kg/m^2, according to country-specific demographics)	Physicians should consider advising/ encouraging patients with obesity, diabetes, and CKD to lose weight, particularly patients with eGFR $\geq$30 ml/min per 1.73 m^2	For adults with overweight and obesity, counseling and caloric restriction are recommended for achieving and maintaining weight loss
Tobacco use (most commonly cigarette smoking)	Individuals should be encouraged to stop smoking	People who use tobacco should be advised to quit using tobacco products	Adults should be assessed at health-care visits for tobacco use, and those who use tobacco should be assisted and strongly advised to quit
Alcohol use (measured by standard alcohol drink per occasion and frequency per week)	No specific recommendations	No specific recommendations	For individuals with hypertension and who drink alcohol, reduce daily alcohol intake to: two or less drinks for men, one or less drink for women

BMI, body mass index.

Lifestyle Behavior Prevalence in CKD

The majority of people with CKD do not adhere to several of the recommended levels of lifestyle behaviors (Figure 1). Two thirds of adults with CKD in the United States do not meet the recommended physical activity levels and are sedentary (7,8). More than three quarters of people with CKD are overweight/obese (9,10). Nearly a half to three quarters of people with CKD do not consume a healthy diet, depending on the definition of the recommended diet (4,6,9). Nonsmoking ranged between 71%–92% from CKD cohorts in Europe, North America, and Japan (11), and, among individuals with CKD in the United States, reports of nonsmoking is similar to that of the general population (approximately 86%) (4,6,9,12,13). Nearly all individuals with CKD (93%) meet alcohol recommendations (6).

Diet and CKD

The role of diet in progression of kidney disease has been of great interest for many decades. There are several guideline recommendations for diet and CKD (Table 2), and numerous studies examining the relationship of dietary components and patterns with clinical outcomes in CKD (Tables 3 and 4). By far, the most studied dietary intervention has been protein restriction. and). The Brenner hyperfiltration theory posits that dietary protein restriction reduces progressive glomerular injury by reducing glomerular hyperfiltration (14). Although protein restriction has been shown to be effective in animal models, the data are mixed in human trials. A 2018 meta-analysis of low protein diets in adults with nondiabetic CKD reported that a low protein intake (0.5–0.6 g/kg per day) versus normal protein intake (≥0.8 g/kg per day) had no effect on risk of ESKD. A very low protein intake (0.3–0.4 g/kg per day) probably reduced the risk of ESKD (relative risk [RR], 0.65; 95% confidence interval [95% CI], 0.49 to 0.85) versus a low or normal protein intake, although there were limited data on adverse effects and no data on quality of life (15) (Figure 2) . As such, the Kidney Disease Outcomes Quality Initiative (KDOQI) 2020 nutrition guidelines recommend, under close clinical supervision, protein restriction with or without keto acid analogues to reduce risk of ESKD/death due to high quality evidence (Table 2). In patients with diabetic CKD, benefits are even less certain (16), with the KDIGO diabetes guideline reporting inconclusive evidence of protein restriction on change in eGFR, ESKD, or other health outcomes (17). The type of protein source may matter because animal-based protein seems to induce higher glomerular hyperfiltration than vegetable-based proteins (18), and a vegetarian diet with equivalent nutrients was shown to result in lower levels of serum phosphate, urine phosphate excretion, and fibroblast growth factor-23 levels (19). Studies in animals have shown that excessive phosphate intake can cause renal parenchymal calcification and proximal tubular injury (20). However, scarce evidence exists that current levels of phosphate intake in humans play a significant role in CKD progression, or that reduction of phosphate intake reduces kidney injury (21–23).

Dietary patterns may be a better way to capture the relationship between diet and chronic disease than studies examining individual nutrients. In addition, dietary patterns may make it easier to provide nutritional advice to patients by focusing on a combination of healthful food groups, rather than focusing on restricting specific nutrients. A systematic review and meta-analysis found that healthy dietary patterns were associated with 27% reduced mortality (n=7 studies; 13,930 participants) but not ESKD (RR, 1.04; 95% CI, 0.68 to 1.40; n=3 studies; 10,071 participants) (24). A study using data from the

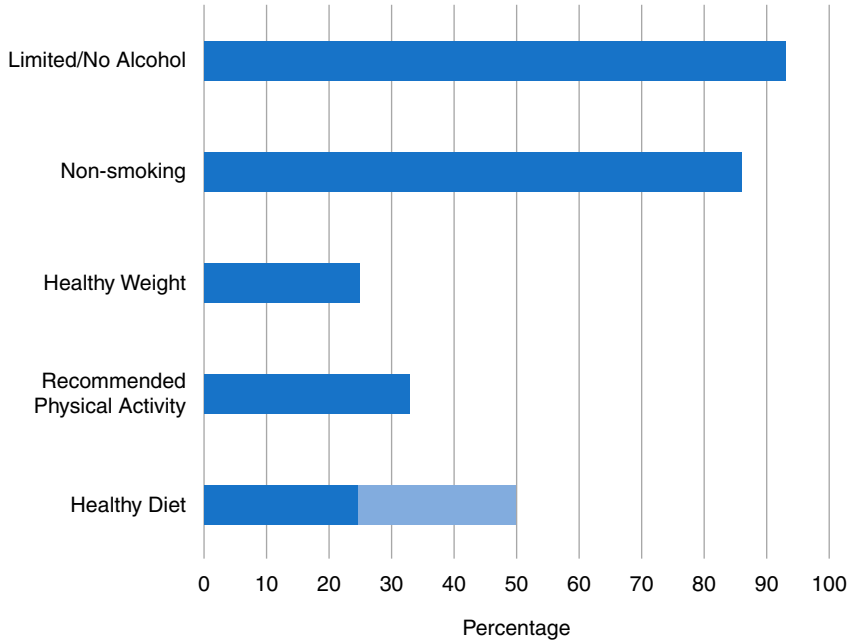

Figure 1. | **The majority of people with CKD do not adhere to several of the recommended levels of lifestyle behaviors.** Estimates from the following published reports: alcohol (6), smoking (4,6,9,12,13), weight (9,10), physical activity (7,8), and diet (4,6,9).

Table 2. Diet recommendations for individuals with CKD

Dietary Component	Recommendation	Source
Dietary pattern	Adults with CKD 1–5 not on dialysis or post-transplantation, with or without dyslipidemia: suggest prescribing a Mediterranean diet may improve lipid profiles (2C)	KDOQI Nutrition 2020 (87)
Protein intake	Adults with CKD 3–5 who are metabolically stable: recommend, under close clinical supervision, protein restriction with or without ketoacid analogues, to reduce risk for ESKD/death (1A) and improve quality of life (2C)	KDOQI Nutrition 2020 (87)
	Adults with CKD 1–5D (1B) or those post-transplantation (OPINION): there is insufficient evidence to recommend a particular protein type (plant versus animal) in terms of the effects on nutritional status, calcium or phosphate levels, or the blood lipid profile	
	Patients with diabetes with CKD 1–5: suggest maintaining a protein intake of 0.8 g protein/kg (weight) per day (2C)	KDIGO Diabetes 2020 (17)
Dietary acid load	Adults with CKD 1–4: suggest reducing NEAP through increased dietary intake of fruits and vegetables (2C) to reduce the rate of decline of residual kidney function	KDOQI Nutrition 2020 (87)
Sodium intake	Adults with CKD 3–5: recommend limiting sodium intake to <2.3 g/d to reduce BP and improve volume control (1B)	KDOQI Nutrition 2020 (87)
	Adults with CKD 3–5: suggest limiting sodium intake to <2.3 g/d to reduce proteinuria synergistically with available pharmacologic interventions (2A)	
	Patients with diabetes with CKD: suggest limiting sodium intake to <2 g/d in patients with diabetes and CKD (2C)	KDIGO Diabetes 2020 (17)
	Patients with high BP and CKD: suggest targeting a sodium intake <2 g/d in patients with high BP and CKD (2C)	KDIGO Blood pressure 2020 (86)
Potassium intake	Adults with CKD 3–5: reasonable to adjust dietary potassium intake to maintain serum potassium within the normal range (OPINION)	KDOQI Nutrition 2020 (87)
Calcium intake	Adults with CKD 3–4 not taking active vitamin D analogues: suggest total elemental calcium intake of 800–1000 mg/d (including dietary calcium, calcium supplementation, and calcium-based phosphate binders) to maintain a neutral calcium balance (2B)	KDOQI Nutrition 2020 (87)
Phosphorus intake	Adults with CKD 3–5: recommend adjusting dietary phosphate intake to maintain serum phosphate levels in the normal range (1B)	KDOQI Nutrition 2020 (87)
	Adults with CKD 1–5: reasonable when making decisions about phosphate restriction treatment to consider the bioavailability of phosphate sources (*e.g.*, animal, vegetable, additives) (OPINION)	

The strength of each recommendation is indicated as Level 1 ("recommended") or Level 2 ("suggested"), and the quality of the supporting evidence is shown as A, B, C, or D: high, moderate, low, and very low, respectively. Opinion is expert opinion without strong evidence in CKD population. KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; NEAP, net endogenous acid production.

National Health and Nutrition Examination Survey (NHANES; 1988–1994) found that a low Dietary Approaches to Stop Hypertension (DASH) dietary score was associated with ESKD (quintile 1 relative hazard, 1.7; 95% CI, 1.1 to 2.7; quintile 2 relative hazard, 2.2; 95% CI, 1.1 to 4.1) (25). Hu *et al.* (26) examined the relationship between dietary intake and risk of CKD progression in the Chronic Renal Insufficiency Cohort (CRIC) Study. Compared with participants with the lowest tertile of adherence, the participants in the most adherent tertile of the Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean diet (aMed), and DASH diet were associated with lower risk of CKD progression (17% for AHEI-2010, 25% for aMed, 17% for DASH).

Observational studies examining associations between specific foods and risk of ESKD have often found conflicting findings and can be challenging to interpret given the different methods of estimating intake and differing approaches to adjustment. In the Singapore Chinese Health Study, red meat intake was associated with ESKD (highest quartile versus lowest quartile, hazard ratio, 1.40; 95% CI, 1.15 to 1.71), whereas the consumption of poultry, fish, eggs, or dairy products was not associated with ESKD (27). In the CRIC Study, the benefits observed with the aMed study were largely driven by vegetable and nut intake, whereas no association was seen with red/processed meat intake (26). In the NHANES study, the association between DASH dietary score and risk of ESKD appeared to be

Table 3. Summary of RCTs of meta-analyses and select large, randomized studies examining diet and CKD progression with at least 100 participants and 12 months of follow-up

Publication Details	Comparators	Sample Description and Follow-Up	Kidney Function (CKD Stages, Mean eGFR: Other Key Inclusion/ Exclusion Criteria)	Intervention Characteristics	CKD Progression Measure(s)	Key Findings/Conclusions
Hahn *et al.* 2018 (15), meta-analysis	LPD versus normal protein	Six trials with N=1814 with ESKD as outcome; eight trials with N=1680 with final or change in GFR as outcome	Stage 3–5 CKD	Included RCTs or quasi-RCTs in which adults with nondiabetic stage 3–5 CKD not on dialysis randomized to LPD versus normal protein intake for ≥12 months	ESKD; end or change in GFR	Compared with normal protein diet, LPD had no or little effect on ESKD (low certainty), with HR, 1.05 (95% CI, 0.73 to 1.53), and uncertain effect on final or change in GFR (very low certainty), with SMD −0.18 (95% CI, −0.75 to 0.38)
Hahn *et al.* 2018 (15), meta-analysis	VLPD versus LPD or normal protein diet	Ten trials with N=1010 with ESKD as outcome; six trials with N=456 with end or change in GFR as outcome; six trials with N=681 with death as outcome	Stage 3–5 CKD	Included RCTs or quasi-RCTs in which adults with nondiabetic stage 3–5 CKD not on dialysis randomized to VLPD versus LPD/ normal protein intake for ≥12 months	ESKD; end or change in GFR	Compared with LPD or normal protein diet, VLPD probably reduced risk of ESKD (moderate certainty; RR, 0.64; 95% CI, 0.49 to 0.85) and uncertain effect on final or change in GFR (very low certainty; SMD, 0.12; 95% CI, −0.27 to 0.52)
KDIGO Diabetes Guideline 2020 (17)	LPD versus normal protein diet	One trial with N=82 for ESKD as outcome (follow-up 4 yr); one trial with N=88 for doubling of creatinine (follow-up 5 yr); two trials with N=170 (follow-up 4.5 yr)	Stage 1–5 CKD and type 1 or 2 diabetes	Included RCTs of patients with stage 1–5 CKD and T1D or T2D comparing low protein diets versus usual diets with kidney outcomes	ESKD; doubling of creatinine	Compared with normal protein diet, LPD had uncertain effect on ESKD (low certainty; RR, 0.47; 95% CI, 0.08 to 2.75) or doubling of serum creatinine (very low certainty; RR, 0.89; 95% CI, 0.37 to 2.15)
Navaneethan *et al.* 2019 (33), meta-analysis	Treatment of metabolic acidosis with dietary acid intake versus control	Six trials with N=1383 with eGFR decline outcome;two trials with N=434 with ESKD outcome	Stage 3–5 CKD; metabolic acidosis (TCO_2 <22) or low-normal bicarbonate (22–24)	Included studies that used dietary intervention (two ketoanalogue-supplemented VLPD, one VLPD, one LPD, one "six-point diet", one fruits/ vegetables) versus control diets (usual diet or LPD)	eGFR decline ESKD	Treatment of metabolic acidosis with dietary acid intake probably reduces risk of eGFR decline (moderate): mean difference, −3.28 (95% CI, −4.42 to −2.14) ml/min per 1.73 m^2 per year and might reduce risk of ESKD (low certainty; RR, 0.32; 95% CI, 0.18 to 0.56)
Garneata *et al.* 2016 (91), Romania	VLPD and KAA versus LPD	N=207 Mean age: 54 yr With diabetes: 0% Follow-up: 15 mo	CKD 4–5; mean eGFR: 18 ml/min per 1.73 m^2; had to agree to follow vegetarian VLPD and KAA during run-in period, proteinuria <1 g/d, and good nutritional status;	VLPD (0.3 g protein/kg ideal body weight per day) and KAA (Ketosteril 0.125 g/ kg ideal dry body weight per day); conventional LPD (0.6 g protein/kg per day);both arms received intensive nutritional counseling and monitoring	RRT or >50% reduction in eGFR	Vegetarian VLPD KAA group had lower risk of RRT or >50% reduction in GFR (13% versus 42%); no safety concerns in terms of anthropometric or biochemical nutritional parameters; only 42% of patients meeting all selection criteria accepted potentially following vegetarian diet

Table 3. (Continued)

Publication Details	Comparators	Sample Description and Follow-Up	Kidney Function (CKD Stages, Mean eGFR: Other Key Inclusion/ Exclusion Criteria)	Intervention Characteristics	CKD Progression Measure(s)	Key Findings/Conclusions
			exclusion criteria included poor compliance, heart/ liver failure	q2wk for 1 month, monthly for 3 months, and then q3 months		
Goraya *et al.* 2014 (34), United States	Fruits/vegetables to reduce dietary acid load by 50% versus sodium bicarbonate 0.3 mEq/kg per day versus usual care	*N*=108 Mean age: 54 yr With diabetes: 0% Follow-up: 3 y	Stage 3 CKD; mean eGFR: 39.5 ml/min per 1.73 m^2; TCO_2 <25 mmol/L; exclusion criteria included K >4.6 mEq/L, primary kidney disease, heart/liver failure, nephrotic syndrome	Fruits and vegetables prescribed by dietitian and distributed from community food bank (sufficient for patient and each of their household member)	eGFR using cystatin C at 3 years	Both the fruit/vegetable (−7.8 ml/ min per 1.73 m^2; 95% CI, −12.15 to −3.45 ml/min per 1.73 m^2) and bicarbonate (−6.0 ml/min per 1.73 m^2; 95% CI, −10.44 to −1.56 ml/ min per 1.73 m^2) groups slowed eGFR decline at 3 years versus control
Cianciaruso *et al.* 2008 (92), Italy	LPD versus normal protein diet	*N*=423 Mean age: 61 yr With diabetes: 12%	Stage 4–5 CKD; mean eGFR 18 ml/min per 1.73 m^2; exclusion criteria included unstable kidney function, malignancy, immu- nosuppression, pro- teinuria >5 g/d	Prescribed low protein diet (0.55 g/kg per d) versus normal protein diet (0.80 g/kg per d); 24-hour urine urea nitrogen every 3 months with dietary guidance by dietitian for all patients	eGFR	No difference in change in eGFR; BUN (primary outcome) lower in low protein group; compliance was 27% in the 0.55 g/kg per day group and 53% in the 0.8 g/kg per day group
Locatelli 1989 (93), Italy	LPD versus normal protein diet	*N*=456 Mean age: 48.5 yr With diabetes: 0% Follow-up: 2 y from start of study	CKD stage 3–5; mean eGFR not reported; exclusion criteria included nephrotic syndrome, systemic diseases, obstructive uropathy	LPD (0.6 g/kg per day); normal protein diet (1 g/ kg per day)	Slope of 1/SCr; ESKD or doubling of creatinine	No difference in ESKD or decline in CrCl; 32% lost by final follow-up
Klahr *et al.* 1994 (94), MDRD study I, United States	LPD versus normal protein diet	*N*=585Mean age: 52 yr With diabetes: 3% Mean follow-up: 2.2 y (mean reported for MDRD Study 1 and 2)	CKD stage 2–3; mean eGFR 38 ml/min per 1.73 m^2; exclusion criteria included body- weight <80% or >160% of standard body weight, DM requiring insulin, kidney transplant,	LPD (0.58 g/kg per day);normal protein diet (1.3 g/kg per day); protein intake assessed monthly with 24-hour urine urea nitrogen	Slope of GFR decline measured by ^{125}I iothalamate; ESKD	LPD had no effect on GFR decline at 3 years; no effect on ESKD

Table 3. (Continued)

Publication Details	Comparators	Sample Description and Follow-Up	Kidney Function (CKD Stages, Mean eGFR: Other Key Inclusion/ Exclusion Criteria)	Intervention Characteristics	CKD Progression Measure(s)	Key Findings/Conclusions
			chronic medical conditions			
Klahr *et al.* 1994 (94), MDRD study II, United States	VLPD and KAA supplement versus LPD diet	*N*=255 Mean age: 52 yrWith diabetes: 3% Follow-up: 2.2 yr (mean reported for MDRD Study 1 and 2)	CKD stage 4–5; mean eGFR 19 ml/min per 1.73 m^2; exclusion criteria included body-weight <80% or >160% of standard body weight, DM requiring insulin, kidney transplant, chronic medical conditions	VLPD (0.28 g/kg per day) plus KAA supplement; LPD (0.58 g/kg per day);protein intake assessed monthly with 24-hour urine urea nitrogen	Slope of GFR decline measured by ^{125}I iothalamate; ESKD	VLPD and KAA tended to slow GFR decline GFR (0.8 ml/min per year less; 95% CI, −0.1 to 1.8 ml/min); no effect on ESKD
Rosman *et al.* 1984 (95), study I, Netherlands	LPD (0.6 g/kg per day) versus normal protein diet	*N*=228 Mean age: 48 yr X% diabetes Follow-up: maximum 18 mo	CKD stage 3; mean eGFR not reported; exclusion criteria included immunologic diseases or cancer, NSAIDs	LPD (0.6 g/kg per day); 24-hour urine urea excretion used to guide therapy by dietitian; normal protein (free diet)	Slope of 1/SCr; ESKD	No effect on ESKD; LPD slowed rate of rate of 1/SCr decline
Rosman *et al.* 1984 (95), study II, Netherlands	VLPD (0.4 g/kg per day) versus normal protein	Netherlands Mean age: 48 yrX% diabetes Follow-up: maximum 18 mo	CKD stage 4–5; mean eGFR not reported; exclusion criteria included immuno-logic diseases or cancer, NSAIDs	LPD (0.6 g/kg per day); normal protein (free diet)	Slope of 1/SCr; ESKD	Decreased risk of ESKD (RR, 0.52; 95% CI, 0.31 to 0.88); VLPD slowed rate of rate of 1/SCr decline

RCT, randomized controlled trial; LPD, low protein diet; HR, hazard ratio; 95% CI, 95% confidence interval; SMD, standardized mean difference; VLPD, very low protein diet; RR, risk ratio; KDIGO, Kidney Disease Improving Global Outcomes; T1D, type 1 diabetes; T2D, type 2 diabetes; TCO_2, total carbon dioxide; KAA, ketoacid analogue; q2wk, every 2 weeks; q3 months, every 3 months; K, potassium; SCr, serum creatinine; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease; DM, diabetes mellitus; ^{125}I, iodine-125; NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Summary of selected observational studies examining diet and CKD progression

Publication Details	Sample Description (Size, Age, Location, % diabetes)	Kidney Function	Dietary Assessment	Key Findings/Conclusions
Dietary patterns				
Hu *et al.* 2021 (26), United States	*N*=2403 Age: 21–74 yr With diabetes: 43% Median follow-up: 12 yr	CKD stages 1–4; mean eGFR: 47 ml/min per 1.73 m^2	Dietary scores (HEI-2015, aHEI-2010, aMed, DASH) calculated using data from FFQ (NCI DHQ) at up to three time points (baseline, year 2, year 4)	Adherence to healthy dietary patterns associated with decreased risk of ESKD or 50% eGFR decline (highest adherence tertile versus lowest adherence tertile for aHEI-2010 [aHR, 0.83; 95% CI, 0.69 to 0.99], aMed [aHR, 0.75; 95% CI, 0.62 to 0.90], DASH [aHR, 0.83; 95% CI, 0.69 to 0.99]; no association for HEI-2015 score [aHR, 0.91; 95% CI, 0.77 to 1.09])
Banerjee *et al.* 2019 (25), United States	*N*=1110 Mean age: 70.2 yr With diabetes: 28% Median follow-up: 7.8 yr	CKD stage 3; mean eGFR: 48.4 ml/min per 1.73 m^2	DASH score calculated using single 24-hour dietary recall	Lowest adherence quintile versus highest adherence quintile associated with higher risk of ESKD (aHR, 2.6; 95% CI, 1.9 to 3.8)
Ricardo *et al.* 2015 (4), United States	*N*=3006 Mean age: 58 yr With diabetes: 45% Median follow-up: 4 yr	CKD stages 1–4; mean eGFR: 43 ml/min per 1.73 m^2	"Healthy diet score" based on five dietary factors from AHA recommendations for CVD health promotion using data from FFQ (NCI DHQ) at baseline	No association between healthy diet score and CKD progression
Gutierrez *et al.* 2014 (96), United States	*N*=3972 Mean age: 68.2 yr With diabetes: 33%	CKD stages 1–5; mean eGFR: 68 ml/min per 1.73 m^2	Empirically derived dietary pattern scores using data from FFQ (block 98 FFQ): "convenience," "plant-based," "Southern," "alcohol/salads"	There were no associations between five empirically derived dietary patterns with incident ESKD
Dietary acid load/net endogenous acid production				
Scialla *et al.* 2012 (31), United States	*N*=632 Mean age: 55 yr With diabetes: not reported Median follow-up: 3.2 yr	CKD stages 2–4; mean eGFR: 46.5 ml/min per 1.73 m^2	NEAP calculated using 24-hour urine urea nitrogen and potassium measured up to four times in first 2 years	Higher NEAP associated with faster decline in iothalamate-measured GFR (Q4 versus Q1, 1.01 ml/min per 1.73 m^2 per year faster decline); ESKD outcome not significant (per 25 mEq/d, HR, 1.10; 95% CI, 0.96 to 1.26)
Banerjee *et al.* 2015 (97), United States	*N*=1486 Mean age: 73 yr With diabetes: 30% Median follow-up: 14.2 yr	CKD stages 3–4; eGFR 15–40 ml/min per 1.73 m^2, 26%; eGFR 40–60 ml/min per 1.73 m^2, 74%	Dietary acid load calculated using single 24-hour dietary recall	Higher dietary acid load associated increased risk of ESKD (tertile 3 versus tertile 1, HR, 3.04; 95% CI, 1.58 to 5.86; tertile 2 versus tertile 1, HR, 1.81; 95% CI, 0.89 to 3.68); risk of ESKD associated with DAL tertiles increased as eGFR decreased (trend P=0.001)
Scialla *et al.* 2017 (32), United States	*N*=980 Mean age: 58 yrWith	CKD stages 1–4; mean eGFR: 44 ml/min per 1.73 m^2	NAE (sum of urinary ammonium and titratable acidity calculated from	Higher NAE associated with decreased risk of composite of ESKD or halving of eGFR in diabetics (aHR, 0.88 per 10 mEq/day higher NAE;

Table 4. (Continued)

Publication Details	Sample Description (Size, Age, Location, % diabetes)	Kidney Function	Dietary Assessment	Key Findings/Conclusions
	diabetes: 51% Median follow-up: 6 yr		urinary pH, phosphate, and creatinine); NEAP calculated using estimated protein and potassium intake on the basis of: (*1*) a single FFQ, and (*2*) a single 24-hour urine collection for urea nitrogen and potassium	95% CI, 0.80 to 0.98), but not in those without diabetes (aHR, 1.04 per 10 mEq/day higher NAE; 95% CI, 0.89 to 1.22). In secondary analyses, higher NEAPurine was associated with the composite outcome (per 10 mEq/d, 1.03; 95% CI, 1.00 to 1.06) in those without diabetes but not in those with diabetes (per 10 mEq/d, 1.00; 95% CI, 0.97 to 1.02). No association between NEAP and ESKD using FFQ
Sodium and potassium				
He *et al.* 2016 (38), United States	*N*=3757 Mean age: 58 yr With diabetes: 48% Total cohort follow-up: 15,807 yr	CKD stages 2–4; mean eGFR: 44.5 ml/min per 1.73 m^2	Mean sodium and potassium of up to three 24-hour urine collections (*N*=2165 with three measurements; *N*=983 with two measurements; *N*=609 with one measurement)	Compared with the lowest quartile of urinary sodium excretion (<116.8 mmol per 24 h), highest quartile of urinary sodium excretion associated with increased risk of CKD progression (HR, 1.54; 95% CI, 1.23 to 1.92); compared with the lowest quartile of urinary potassium excretion, highest quartile of urinary potassium excretion associated with increased risk of CKD progression (HR, 1.59; 95% CI, 1.25 to 2.03)
Leonberg-Yoo *et al.* 2017 (98), United States	*N*=840 Mean age: 52 yr With diabetes: 5% Median follow-up: 19.2 yr	CKD stages 3–5; mean eGFR: 32.6 ml/min per 1.73 m^2	24-Hour urine potassium measured at baseline and in sensitivity analysis every month (median number of urine collections, 24)	No association between baseline urine potassium and kidney failure (per 1-SD increase, aHR, 0.95; 95% CI, 0.87 to 1.04); similar findings using time-averaged potassium
Koo *et al.* 2018 (39), South Korea	*N*=2238 Age: 55 yr With diabetes: 25% Median follow-up: not reported	CKD stages 1–5; mean eGFR: 51.1 ml/min per 1.73 m^2	Single 24-hour urine sodium and potassium	Compared with lowest quartile of Na/K ratio, there was increased risk of 50% eGFR decline or ESKD in the highest quartile of Na/K ratio (aHR, 2.95; 95% CI, 1.56 to 5.81) and the second highest quartile of Na/K ratio (aHR, 2.48; 95% CI, 1.30 to 4.90)
Kim *et al.* 2019 (99), South Korea	*N*=1821 Mean age: 55 yr With diabetes: 34% Total cohort follow-up: 5326 person-years	CKD stages 1–5; mean eGFR: 47 ml/min per 1.73 m^2	Single urine potassium/creatinine ratio (*n*=1821); 24-hour urine potassium (*n*=855)	Compared with the highest quartile of each potassium measure, low potassium excretion was associated with increased risk of ESKD or 50% eGFR decline measured by spot urine potassium/creatinine ratio (aHR, 1.47; 95% CI, 1.01 to 2.12) and by 24-hour urine potassium (aHR, 3.05; 95% CI, 1.54 to 6.04)

HEI-2014, Healthy Eating Index 2014; aHEI-2010, Alternative Healthy Eating Index 2010; aMed, alternate Mediterranean diet; DASH, Dietary Approaches to Stop Hypertension; FFQ, food frequency questionnaire; NCI, National Cancer Institute; DHQ, Diet History Questionnaire; aHR, adjusted hazard ratio; AHA, American Heart Association; CVD, cardiovascular disease; NEAP, net endogenous acid production; Q4, quartile 4; HR, hazard ratio; DAL, dietary acid load; NAE, net acid excretion; NAEPurine, net acid excretion of purine; Na, sodium; K, potassium.

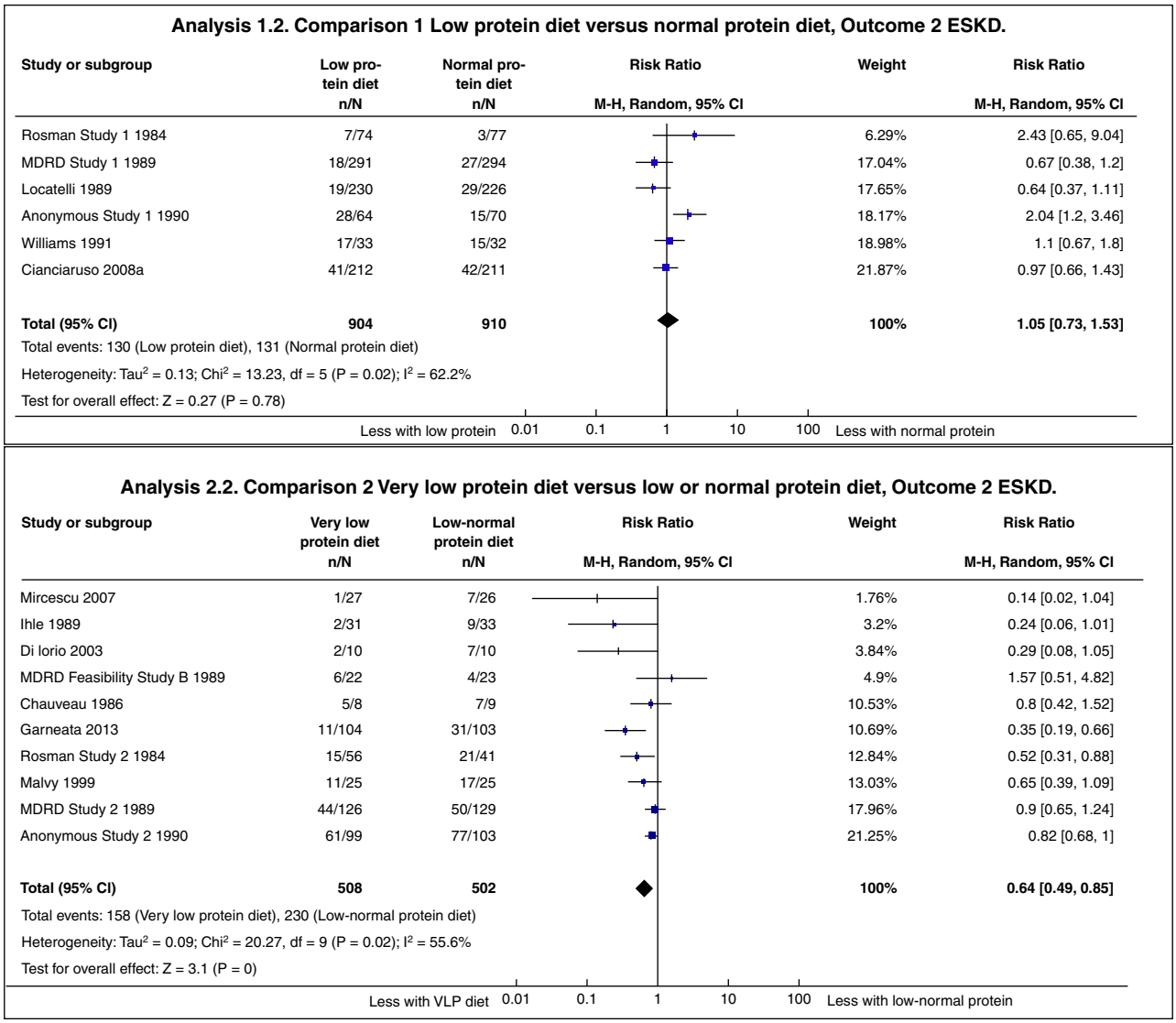

Figure 2. | Among nondiabetics with CKD, low protein intake had no effect on risk of ESKD and very low protein intake probably reduced risk of ESKD. Reprinted from ref. 15, with permission. IV, inverse variance; M–H, Mantel–Haenszel; MDRD, Modification of Diet in Renal Disease; VLP, very low protein.

mediated, in part, by dietary potassium and magnesium, and, to a lesser extent, to dietary acid load (25).

High net endogenous acid production has been theorized to contribute to kidney disease progression by causing net acid retention, which is associated with increased kidney levels of endothelin-1, and markers of kidney and bone injury (28). The most acid-producing foods tend to be sulfur-rich foods, such as hard/processed cheeses, egg yolks, meat, poultry, and fish, because sulfur is oxidized to inorganic sulfate (29). By contrast, fruits and vegetables are rich in citrate and malate, which undergo combustion internally to produce bicarbonate.

Wesson *et al.* (30) have shown that metabolic acidosis could lead to inflammation and fibrosis. Observational studies have shown an association between dietary acid load and risk of ESKD in NHANES (25), and eGFR decline in the African American Study of Kidney Disease and Hypertension (31). However, these studies used estimates of acid load or net acid excretion. In a recent analysis of the CRIC Study, net acid excretion was measured as the sum of urine ammonium and titratable acidity in 24-hour urine samples of a 980-participant subcohort (32). Surprisingly, higher net acid excretion was associated with decreased risk of a composite outcome of ESKD or 50% eGFR decline in patients with diabetes, whereas no association was found in those without diabetes (Table 4). Reasons for this discrepancy are unclear, but the authors hypothesized there may be diet-independent changes in acid production in diabetes (32). Regardless, interventions reducing net endogenous acid production appear to be beneficial for slowing CKD progression. A systematic review of interventions that treat metabolic acidosis (oral alkali therapy or dietary acid reduction) in stage 3–5 CKD found evidence of low-to-moderate certainty that treatment of metabolic acidosis with oral alkali therapy or dietary acid reduction may slow the rate of eGFR decline or reduce the risk of

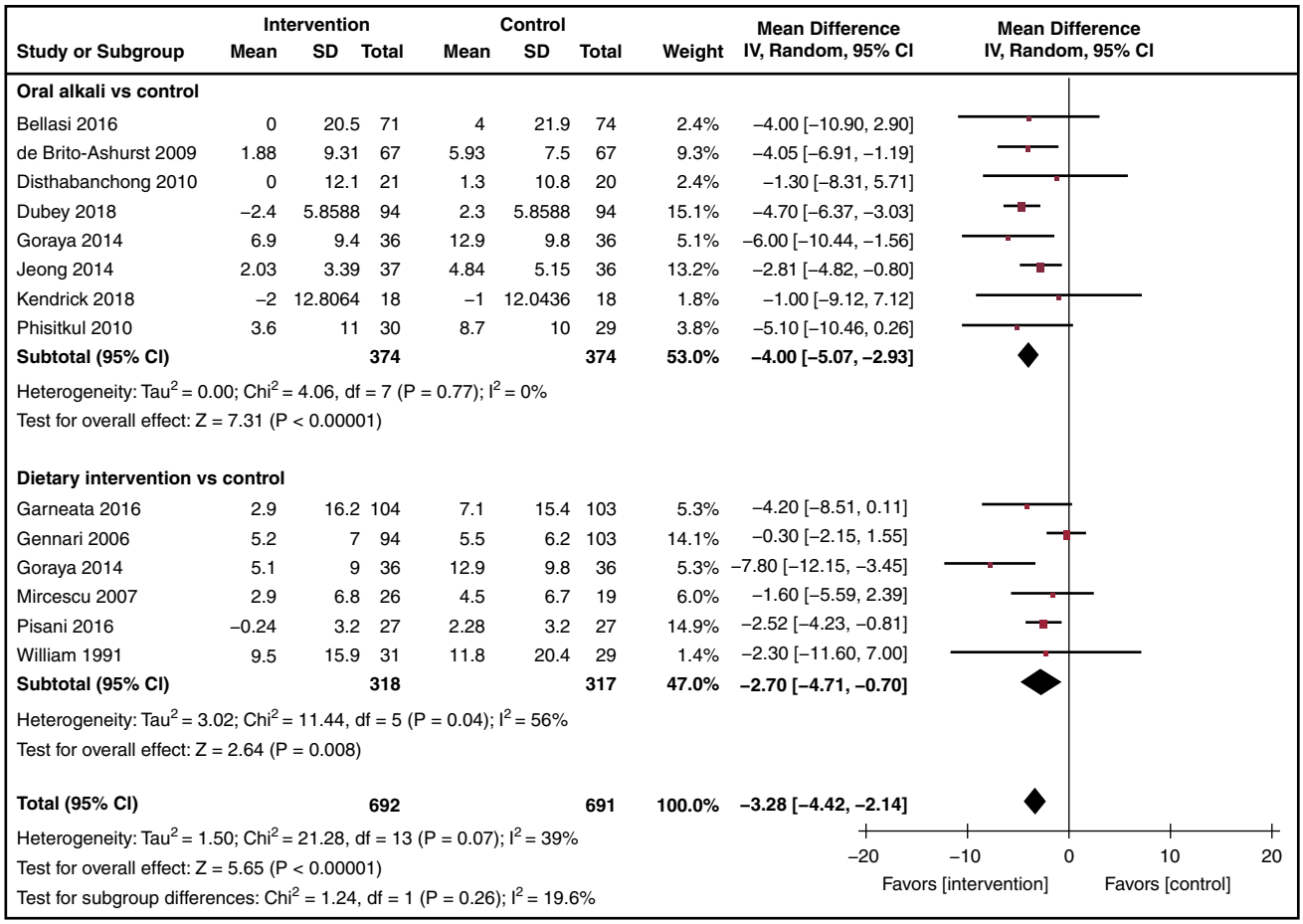

Figure 3. | **Among studies of people with stage 3–5 CKD, there was low-to-moderate evidence that treatment of metabolic acidosis with oral alkali therapy or dietary acid reduction slowed the rate of eGFR decline or reduced the risk of ESKD.** Reprinted from ref. 33, with permission. IV, inverse variance.

ESKD (33) (Figure 3) . In a small RCT of 108 patients with stage 3 CKD and bicarbonate levels of 22–24 mmol/L, randomization to alkali therapy, whether delivered as sodium bicarbonate or by providing fruits and vegetables, slowed cystatin C–based eGFR decline over 3 years (34). The KDOQI 2020 nutrition guidelines suggest, based on limited evidence, that increasing intake of fruits and vegetables can reduce net endogenous acid production to slow CKD progression (Table 2).

Limited data exist on sodium and potassium intake and CKD progression. Capturing dietary sodium and potassium intake is challenging because collecting multiple-day, 24-hour urine collections or diet records can be burdensome and food frequency questionnaires can be limited if questions are not applicable to local dietary practices; both food frequency questionnaires and 24-hour diet recalls are limited by recall bias. Multiple 24-hour urine collections are the gold standard for estimating sodium intake (35), although there have not been validation studies of 24-hour urine sodium and potassium versus measured dietary intake specifically in patients with CKD. RCTs comparing different levels of sodium intake suggest that sodium reduction lowers albuminuria (36,37), and observational studies (CRIC Study, KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease [KNOW-CKD]) have reported an association between high 24-hour urine sodium and increased risk of CKD progression (Table 4). Data on potassium are mixed, with high 24-hour urine potassium excretion being associated with CKD progression in CRIC, whereas low 24-hour urine potassium excretion was associated with CKD progression in KNOW-CKD (38,39). Unfortunately, there are not yet any long-term RCT data to determine whether modulating either sodium or potassium intake affects CKD progression. A multicenter, double-blind, placebo-controlled RCT testing the effects of 40 mEq of potassium (delivered as potassium chloride or potassium citrate) versus placebo on eGFR decline in patients with hypertension and stage 3b/4 CKD is currently underway (https://clinicaltrials.gov/ct2/show/NCT03253172) (40).

Specific types of CKD may have particular benefits to dietary modification. For example, although an RCT of coaching to increase water intake in patients with stage 3 CKD and albuminuria over 1 year reported no significant effect on kidney function decline (41), there may be benefits in patients with adult autosomal dominant polycystic kidney disease (ADPKD) (42). Increased antidiuretic hormone (arginine vasopressin) stimulates cell proliferation through the vasopressin V2 receptor, resulting in increased

intracellular cAMP. Interestingly, high water intake decreases urinary vasopressin, whereas high sodium intake stimulates urinary vasopressin (43). A recent study found that every 1 g/d of sodium was associated with increased eGFR decline (−0.11 ml/min per 1.73 m^2 per gram of salt), whereas protein intake was not associated with CKD progression in patients with ADPKD. The association between sodium intake and CKD progression was substantially mediated by plasma copeptin, supporting the possible role of sodium increasing vasopressin and resulting in CKD progression (42). Further randomized trials are needed to determine whether sodium restriction or increased fluid intake can slow progression in ADPKD.

Physical Activity and CKD

There is little controversy regarding the beneficial effects of physical activity on overall health and, thus, the Physical Activity Guidelines for Americans recommends adults should move more and sit less throughout the day and participate in any amount of moderate-to-vigorous physical activity to gain some health benefits. For substantial health benefits, adults should do at least 150 minutes of moderate-intensity activity per week or 75 minutes of vigorous-intensity activity per week. Adults should also do strengthening activities of moderate or greater intensity on ≥2 days a week because these activities provide additional health benefits (44). The term exercise is typically applied to moderate or vigorous physical activities (44).

Depending on how physical activity is defined (see Box 1), many adults with CKD have self-reported sedentary behavior and most do not reach recommended levels of physical activity (4,5,8,9, 45). Reduced physical activity is associated with increased mortality (5) and more CVD events (6), but less is known about its relationship to CKD progression, with much of the research stemming from single-center observational studies and very few clinical trials (Table 5) (46). Robinson-Cohen, *et al.* (45) described the relationship between self-reported leisure-time physical activity and kidney function decline in 256 outpatients with stage 3–4 CKD (mean age, 61 years). Nearly a quarter of the patients reported no leisure-time activity at all, and they had a greater decline in eGFR per year compared with those who met the guideline-recommended levels of physical activity. Further, each 60 minute–greater duration of leisure-time physical activity was associated with a 0.5% per year slower decline in eGFR, but leisure-time activity was not associated with incident ESKD (45). Leisure-time physical activity was also not associated with rapid kidney function decline (>3 ml/min per year) among 558 older adults with an eGFR of <60 ml/min per 1.73 m^2 (47). Walking and participation in physical activity more than one time per week in older adults (mean age, >70 years) has been reported to be associated with reduced risk of incident ESKD (48), but, in a younger cohort of people with CKD, recommended physical activity, compared with inactivity, was not associated with a composite CKD progression outcome (50% decline in eGFR from baseline or incident ESKD) (4). Together, these findings suggest that greater leisure-time physical activity may slow the rate of kidney function decline, and that any physical activity may be beneficial for lowering the risk of ESKD, particularly among older adults. However, due to the observational design and heterogeneous definitions for CKD progression, these studies cannot establish causality, and it is possible that physical activity is a marker of overall morbidity and could be confounded by survival bias or competing risk of CVD events in younger individuals. More data are needed to further assess the relationship of physical activity and, particularly the minimum amount needed to slow CKD progression.

Box 1. Physical Activity Intensity and Classifications of Activity

Intensity: Effort required to perform an activity. Aerobic intensity is typically expressed as rate of energy expenditure using kilocalories per minute or metabolic equivalent of task (MET). One MET is equivalent to sitting at rest.
Sedentary: Activity ≤1.5 METs while sitting, reclining or lying down.
Light intensity: Nonsedentary activities while awake, 1.6 to <3.0 METs (*e.g.*, walking at leisurely pace).
Moderate intensity: Activities 3 to <6 METs (*e.g.*, walking briskly, swimming).
Vigorous intensity: Activities ≥6 METs (*e.g.*, walking very fast, running).
Inactive: No moderate- or vigorous-intensity physical activity beyond daily life activities per week.
Insufficiently active: One to <150 min/wk of moderate-intensity physical activity or 1 to <75 min/wk of vigorous-intensity activity per week, or equivalent combination.
Active: Moderate-intensity activity for ≥150 min/week, or equivalent combination of moderate and vigorous (meets guidelines at this level).

Directly assessing the effects of physical activity on CKD progression in patients with established CKD requires RCTs of physical activity or exercise training programs. Two recent meta-analyses investigated the effect of RCTs testing physical activity and exercise interventions on CKD progression among people with CKD, and both meta-analyses found that the interventions were not associated with reduced CKD progression, in terms of no difference in eGFR (Figure 4) (49,50), serum creatinine (49), or proteinuria (50) between intervention and control groups. However, RCTs included in these meta-analyses consisted of small sample sizes, were of short duration, and did not have adequate observation time to evaluate the effect of risk of disease progression. In addition, serum creatinine correlates with muscle mass, which poses a challenge in interpreting small increases in creatinine during an exercise trial due to increased physical activity and increased muscle metabolism, leading to an underestimation of eGFR and, therefore, kidney function.

Weight Management and CKD

In clinical practice, weight management is typically assessed with body mass index (BMI), determined by body weight and height (in kilograms per meter squared). The World Health Organization considers a BMI of between

Table 5. Summary of select epidemiologic studies of the association between physical activity and CKD progression among individuals with established CKD

Publication Details	Sample Description and Follow-Up	Kidney Function (CKD Stages, Mean eGFR)	Definition of PA	CKD Progression Measure(s)	Key Findings of Adjusted Analyses
Observational studies					
Robinson-Cohen *et al.*2009 (47), United States	*N*=558 Age: all >65 yr Median follow-up: 7 yr	Kidney function only reported <60 ml/min per 1.73 m^2	Self-report of leisure-time PA, converted to kilocalories per week	Rapid kidney function decline (>3 ml/min per year) using cystatin C–eGFR	PA was not significantly associated with rapid decline in kidney function
Muntner *et al.* 2013 (9), United States	*N*=3093 Age: mean 72.2 yr With diabetes: 35% Median follow-up: 4 yr	eGFR 47 ml/min per 1.73 m^2 (CKD-EPI)	Self-report of PA and categorized into levels: no PA per week, intermediate (1–3 times per week), ideal (≥4 times per week)	Incident ESKD (dialysis or kidney transplant)	Compared with no PA, intermediate and ideal PA were associated with reduced risk of ESKD (aHR, 0.66 [95% CI, 0.46 to 0.94] and 0.50 [95% CI, 0.32 to 0.78], respectively)
Chen *et al.* 2014 (48), China	*N*=6363 Age: mean 70 yr With diabetes: 42% Median follow-up: 1.3 yr	Stage 3 (36%); stage 4 (20%); stage 5 (44%)	Self-report of walking in last 3 months; categorized into frequency (0, 1–2, 3–4, 5–6, ≥7 times) and duration of activity	Incident ESKD (dialysis or kidney transplant)	Walking was associated with lower ESKD risk (aHR, 0.79; 95% CI, 0.73 to 0.85), and significant trend with lower risk with more frequent walking
Robinson-Cohen *et al.* 2014 (45), United States	*N*=256 Mean age: 61 yr With diabetes: 54% Median follow-up: 3.7 yr	CKD 3–5; mean eGFR range: 37.6–43.9 ml/min per 1.73 m^2	Self-report of leisure-time PA in past 4 weeks (converted to minutes per week) and categorized into none, 1–60, 60–150 and >150 min/wk	Cystatin C–eGFR change per year; incident ESKD	Each 60-minute greater duration of weekly PA was associated with 0.5% per year slower decline in eGFR (P=0.04);PA was not associated with incident ESKD

Table 5. (Continued)

Publication Details	Sample Description and Follow-Up	Kidney Function (CKD Stages, Mean eGFR)	Definition of PA	CKD Progression Measure(s)	Key Findings of Adjusted Analyses
Ricardo *et al.* 2015 (4), United States	*N*=3006 Mean age: 58 yr With diabetes: 45% Median follow-up: 4 yr	Mean eGFR: 43 ml/min per 1.73 m^2 (Cr and cystatin C CRIC-specific equation)	Self-reported moderate and vigorous PA (converted to minutes/week) and categorized as ideal (moderate ≥150 min/wk, vigorous >75 min/wk, or moderate plus vigorous ≥150 min/wk), less than ideal (>0 min/wk but not ideal), and inactive (0 min/wk)	Composite of 50% decrease in eGFR from baseline or incident ESKD	Ideal PA, compared with inactivity, was not associated with CKD progression
Meta-analyses of exercise RCTs on kidney function	Included Trials	Comparators		CKD Progression Measure(s)	Key Findings
Nakamura *et al.* 2020 (49)	Nine trials with *N*=459 with eGFR as outcome;five trials with *N*=231 with serum creatinine as outcome	Included RCTs comparing interventions of physical exercise (center based, home based, combined exercise) with usual care		eGFR; serum Cr	Effect of exercise training on eGFR was not significant compared to usual care (SMD, −0.34; *P*=0.67; moderate-low certainty); effect of exercise training on serum creatinine was not significant compared to usual care (SMD, 1.48; *P*=0.75; low certainty)
Villanego *et al.* 2020 (50)	11 trials with *N*=429 with eGFR as outcome; six trials with *N*=182 with proteinuria as outcome	Included RCTs comparing intervention that included an exercise component (aerobic and strength training) with a control group without physical exercise		eGFRproteinuria (24-h urine protein and albumin-creatinine ratio)	No differences in eGFR between intervention and control groups (SMD, −0.14; *P*=0.90; moderate-low certainty); no differences in proteinuria between intervention and control groups (SMD, 26.2; *P*=0.82; low certainty)

PA, physical activity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aHR, adjusted hazard ratio; Cr, creatinine; CRIC, Chronic Renal Insufficiency Cohort; RCT, randomized controlled trial; SMD, standardized mean difference.

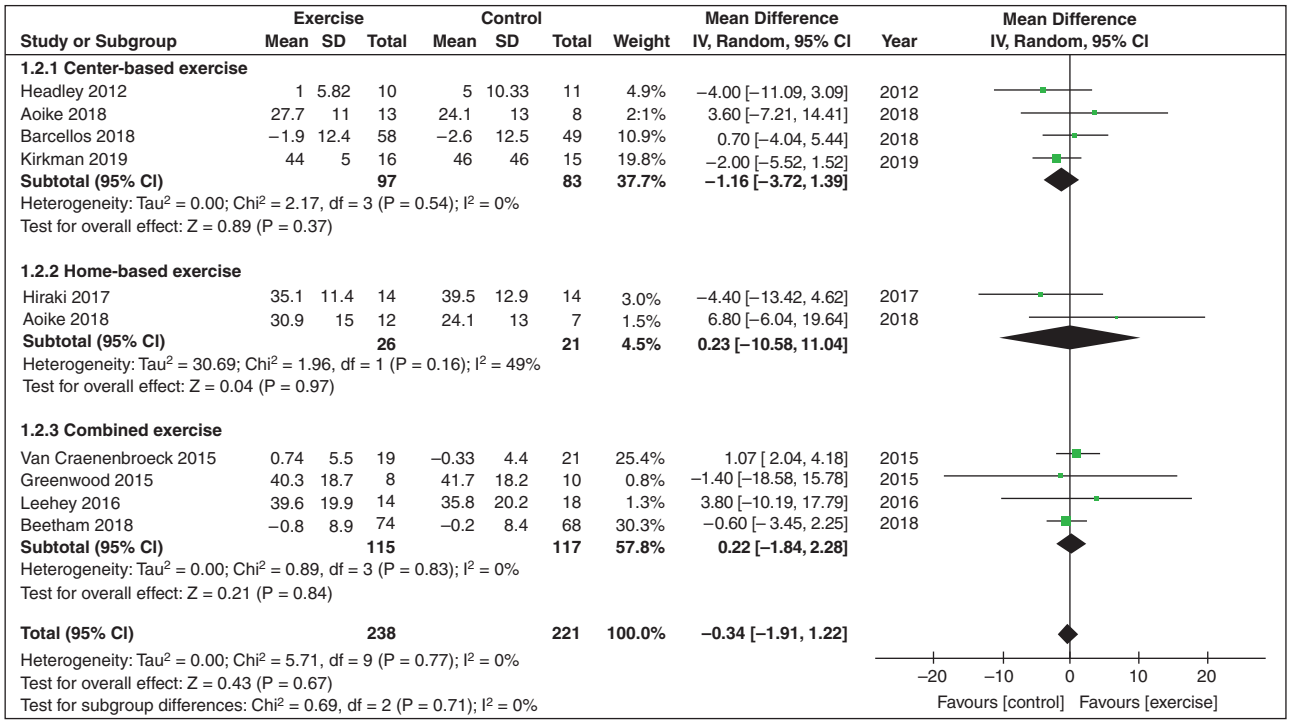

Figure 4. | **A meta-analysis of physical activity and exercise interventions tested in randomized controlled trials among people with CKD found there was no difference in eGFR among intervention and control groups.** Reprinted from ref. 49, with permission.

18.5 and 25 kg/m^2 as normal weight, a BMI between 25 and 30 kg/m^2 as overweight, and a BMI of >30 kg/m^2 as obese. The prevalence of obesity continues to increase worldwide, and a consistent, graded relationship between obesity and incident CKD has been demonstrated (11,51,52). A recent UK Biobank study using Mendelian randomization suggests that the obesity-CKD relationship is causal and mostly mediated by diabetes and elevated BP (53). However, the relationship between obesity and CKD progression is less clear in patients with established CKD (Table 6).

In a large cohort of 453,946 US veterans with an eGFR of <60 ml/min per 1.73 m^2, a BMI corresponding to overweight/mild obesity (25–35 kg/m^2) had the lowest risk for CKD progression, and a BMI <25 kg/m^2 was consistently associated with worsening of kidney function (10). However, the generalizability of this study's findings may be limited because the cohort was older (>70 years), and most participants were men. Individual-level meta-analyses were conducted by the CKD Prognosis Consortium in 5.5 million adults in 39 general population cohorts and 91,607 adults in 18 CKD cohorts (11). In models stratified by baseline eGFR, hazard ratios for risk of eGFR decline for a BMI of 35 kg/m^2 versus a reference BMI of 25 kg/m^2 were 1.88 (95% CI, 1.69 to 2.08) for those with an eGFR of 30–59 ml/min per 1.73 m^2 were 1.78 (95% CI, 1.36 to 2.34) and 1.88 (95% CI, 1.61 to 2.18) for those with an eGFR of <30 ml/min per 1.73 m^2 (Figure 5). Adjustment for potential mediators (*e.g.*, hypertension, diabetes, albuminuria) attenuated results. Meta-analysis of participants in the CKD cohorts found smaller effect sizes, with sensitivity analysis excluding the first 3 years of follow-up suggesting some role of reverse causation (Figure 5, Table 6). Risks associated with obesity may vary by type of kidney disease. An elevated BMI among individuals with IgA nephropathy and ADPKD has been noted as a risk factor for CKD progression (54,55), whereas no association between elevated BMI and risk of CKD progression was noted in a cohort of patients with biopsy sample–proven glomerulonephritides (56).

CKD management guidelines recommend weight reduction for adults with CKD and obesity. However, intentional weight loss among these individuals has shown mixed results, and largely depends on the type of weight-loss intervention (*e.g.*, diet, exercise, surgery, medications). The current evidence of the effects of weight loss on the progression of CKD is mainly on the basis of observational reports and a few small randomized trials of low-to-moderate quality. Bariatric surgery has most consistently suggested a beneficial effect of weight loss on kidney function (57), with a recent RCT of patients with type 2 diabetes and albuminuria demonstrating greater resolution of albuminuria in those undergoing Roux-en-Y gastric bypass versus best medical treatment (82% versus 48% remission) (58). At this time, there are no convincing data to support a specific diet for weight loss to slow CKD progression (59). Additionally, some controversy exists in more advanced CKD (*i.e.*, eGFR of <30 ml/min per 1.73 m^2) because malnutrition and muscle wasting are potential concerns and observational studies have found an association between weight loss and risk of death in patients with ESKD (60–62). However, much of this weight loss is unintentional, and recent studies have found that bariatric surgery is associated with reduced risk of death in patients with CKD and ESKD (63,64). It is beyond the scope of this review to describe in detail each of the weight-loss strategies and CKD

Table 6. Summary of select epidemiologic studies of the association of BMI and CKD progression among individuals with established CKD

Publication Details	Sample Description and Follow-Up	Kidney Function	Obesity Measure	CKD Progression Measure(s)	Key Findings
Hsu *et al.* 2006 (52), United States	*N*=unclear; source population 320,252 with and without CKD; unclear how many with eGFR <60 ml/min per 1.73 m^2Age: 31–43 yr (across categories of weight)With diabetes: 13%–21% (across categories of weight)Follow-up: from 1964 to 1985 until 2000	Individuals with eGFR <60 ml/min per 1.73 m^2 (MDRD) or with presence of proteinuria or hematuria on urinalysis	BMI categories: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), class 1 obesity (30–34.9 kg/m^2), class 2 obesity (35–39.9 kg/m^2), and extreme obesity (≥40 kg/m^2)	Incidence of ESKD (dialysis or transplant)	Compared with normal weight, overweight/obesity associated with increased risk of ESKD in models adjusted for demographics, smoking, myocardial infarction, cholesterol, creatinine, proteinuria, hematuria: BMI 25–29.9 kg/m^2 (RR, 1.5; 95% CI, 1.2 to 2.0), BMI 30–34.9 kg/m^2 (RR, 2.7; 95% CI, 2.0 to 3.6), BMI 35–39.9 kg/m^2 (RR, 4.7; 95% CI, 3.3 to 6.8), BMI ≥40 kg/m^2 (RR, 3.1; 95% CI, 1.8 to 5.3)
Babayev *et al.* 2013 (100), United States	*N*=12,534 participants of National Kidney Foundation Kidney Early Evaluation ProgramMean age: 66.8 yrWith diabetes: 42%Follow-up: 8 yr	CKD stages 3–4;mean eGFR: 48 ml/min per 1.73 m^2 (CKD-EPI)	BMI categories: <30 kg/m^2, 30–34.9 kg/m^2, ≥35 kg/m^2	Incident ESKD	Compared with BMI <30 kg/m^2, obesity not associated with ESKD in models adjusted for demographics, hypertension, diabetes, eGFR, and albuminuria: BMI 30–34.9 kg/m^2 (HR, 0.90; 95% CI, 0.65 to 1.25); BMI ≥35 kg/m^2 (HR, 1.09; 95% CI, 0.78 to 1.52)
Lu *et al.* 2014 (10), United States	*N*=453,946 US veterans with eGFR <60 ml/min per 1.73 m^2Age: 73.9 yrWith diabetes: 41%Follow-up: from 2004 to 2006 until 2012	Mean eGFR: 47.9 ml/min per 1.73 m^2 (CKD-EPI)	BMI categories: <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, 40 to <45, 45 to <50, and ≥50 kg/m^2	Incident ESKD; doubling of serum creatinine; slopes of eGFR	BMI between 25–35 kg/m^2, corresponding to overweight/mild obesity, had lowest risk of CKD progression. In models adjusted for demographics, comorbidities (except for hypertension, diabetes), medications, BMI ≥35 kg/m^2 associated with worse outcomes in patients with stage 3 CKD, but not in stage 4–5 CKD; additional adjustment for hypertension and diabetes attenuated associations
Yun *et al.* 2018 (101), South Korea	*N*=1940 participants of KNOW-CKDAge: 53.5 yrWith diabetes: 34%Median follow-up: 3.1 yr	CKD 1–5; mean eGFR: 54.1 ml/min per 1.73 m^2 (CKD-EPI)	Obesity defined as BMI ≥25 kg/m^2	Composite of 50% decline in eGFR from baseline or onset of ESKD (dialysis or kidney transplant)	Compared with nonobesity, obesity was associated with increased risk of CKD progression. In model adjusted for demographics, smoking, laboratory measures, left ventricular mass index, eGFR, proteinuria: obesity was associated with HR of 1.41 (95% CI, 1.08 of 1.83)
Chang *et al.* 2019 (11), individual-level meta-analysis	39 general population cohort studies (*N*=5,459,014)Mean follow-up: 6 yr	Individuals with eGFR <60 ml/min per 1.73 m^2	Continuous BMI with linear splines	GFR decline determined by estimated eGFR decline ≥40%, initiation of RRT or eGFR <10 ml/min per 1.73 m^2	Among patients with eGFR <60 ml/min per 1.73 m^2 in general population cohorts, J-shaped association between BMI and risk for GFR decline with significant heterogeneity across cohorts; in models adjusted for demographics and smoking, compared with a BMI of 25 kg/m^2, HRs at 35 kg/m^2: eGFR 30–59 ml/min per 1.73 m^2 (HR, 1.78; 95% CI, 1.36 to 2.34); eGFR <30 ml/min per 1.73 m^2 (HR, 1.88; 95% CI, 1.61 to 2.18);adjustment for

Table 6. (Continued)

Publication Details	Sample Description and Follow-Up	Kidney Function	Obesity Measure	CKD Progression Measure(s)	Key Findings
					potential mediators attenuated association (moderate certainty)
Chang *et al.* 2019 (11), individual-level meta-analysis	18 cohort studies with participants with CKD (*N*=91,607)Mean follow-up: 4 yr	Mean eGFR range: 22–75 ml/min per 1.73 m^2 across cohorts	BMI categories: 20, 25, 30, 35, 40, 45 kg/m^2	GFR decline determined by estimated eGFR decline ≥40%, initiation of RRT or eGFR <10 ml/min per 1.73 m^2	J-shaped association between BMI and risk for GFR decline with significant heterogeneity across cohorts; in model adjusted for demographics and smoking, compared with BMI 25 kg/m^2, HR at 35 kg/m^2 was 1.17 (95% CI, 1.04 to 1.31); excluding first 3 years of follow-up, magnified association (HR, 1.75; 95% CI, 1.30 to 2.37), suggesting reverse causation; adjustment for potential mediators attenuated association (moderate certainty)

BMI, body mass index; MDRD, Modification of Diet in Renal Disease; RR, relative risk; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; HR, hazard ratio; KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease.

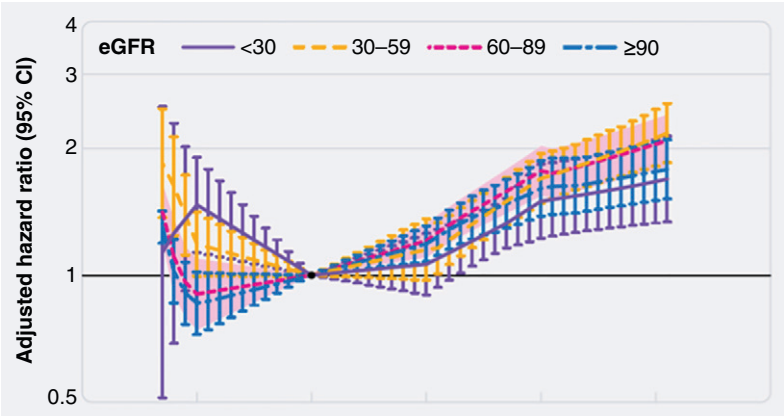

Figure 5. | Individual-level meta-analyses found the risk of eGFR decline was higher among those with BMI 35 kg/m^2, particularly with eGFR <60 ml/min per 1.73 m^2. Meta-analyzed hazard ratios and 95% CIs are related to body mass index, modeled by linear splines with knots at body mass indices of 20, 25, 30, and 35 kg/m^2 (reference is body mass index of 25 kg/m^2 in each category). Reprinted from ref. 11, with permission.

progression; others have provided in-depth reviews of weight-loss strategies that have been used in CKD studies (65,66).

Tobacco Use and CKD

Tobacco use is the leading preventable cause of death and disability in the United States and is a major contributor to CVD (67), which is more common among those with CKD than those without kidney disease. Smoking is associated with increased risk of progression of CKD in some, but not all, studies, and the beneficial effects of smoking cessation on delaying CKD progression is unclear (Table 7) (68,69). Current cigarette smokers, compared with nonsmokers, have been found to have greater eGFR decline per year among those with early-stage CKD and type 2 diabetes (70), or biopsy sample–proven glomerular disease (71), but smoking has not been associated with rapid eGFR decline (>1 ml/min per 1.73 m^2 per year) among those with stage 3 CKD and ADPKD (72). In terms of incident ESKD, smoking was observed to have a higher risk in a study of 1722 people with CKD stage 3 (73), but, among larger cohorts (N=3093 and N=6245) of people with similar levels of kidney function (9,13), smoking was not found to be associated with ESKD.

Former and/or current smoking has been associated with increased risk of a composite outcome of incident ESKD and 50% decline in eGFR in some, but not all, studies—depending on how the smoking exposure was modeled (Table 7). This is exemplified in two studies, using the same data from 3939 adults with an eGFR of 20–70 ml/min per 1.73 m^2 in the CRIC Study, that observed current smoking did and did not have an increased risk of CKD progression when modeled from baseline exposure or as cumulative average exposure, respectively (4,74). The inconsistencies of smoking and CKD progression risk may be attributed to the observational nature of most of the smoking research in CKD, including the study design and population, such as differences in age (which could introduce survival bias), proportion with diabetes, and length of follow-up time to observe the outcome of interest.

There appears to be a dose-response relationship of greater smoking exposure and CKD progression in that higher smoking pack-years were associated with increased CKD progression. In a cohort of 1951 middle-aged adults with predominantly CKD stage 3 (Mean eGFR: 53 ml/min per 1.73 m^2) from the KNOW-CKD Study, ≥15 pack-year smokers and ≥30 pack-year smokers, compared with never smokers, were each associated with increased risk of CKD progression over 3 years of follow-up (75).

The benefits of smoking cessation on CKD progression have not been well studied but appear to be promising. Several studies have shown that the risk for CKD progression of former smokers was lower than that of current smokers (76,77), and there was a graded decrease in risk as time since smoking cessation increased (78). There has been one clinical trial of 108 smokers and 108 nonsmokers with stage 2 CKD and proteinuria without diabetes treated with angiotensin-converting enzyme inhibitor therapy where the current smokers underwent a smoking-cessation intervention program. After 5 years of follow-up, eGFR was higher in nonsmokers and quitters than in continued smokers (79). The use of electronic cigarettes as a means to quit cigarette smoking is not currently supported because the data on the use of electronic cigarettes in those with kidney disease are sparse.

Alcohol Use and CKD

In the general population, alcohol use is associated with poorer health overall, but moderate drinking appears to be protective for some CVD events (80–84). It is proposed that alcohol consumption has cardioprotective effects on insulin sensitivity, thrombotic activity, and inflammation (85). However, among people with established CKD, no or moderate alcohol intake, compared with excessive intake, has been associated with increased risk of major coronary events (6). Similarly, the epidemiologic literature on alcohol and kidney function, which has focused on both the development and progression of kidney disease, has reported mixed observations, largely due to very few studies specifically investigating the relationship of alcohol consumption and the effect on disease progression among individuals

Table 7. Summary of select epidemiologic studies of the association of smoking and CKD progression among people with established CKD

Publication Details	Sample Description and Follow-Up	Kidney Function	Definition of Smoking	CKD Progression Measure(s)	Key Findings of Adjusted Analyses
Orth *et al.* 1998 (102)	Matched pairs: IgA-GN (N=54), ADPKD (N=48) Mean age: 47 (patients) and 49 (controls) yr among men, 48 (patients) and 51 (controls) yr among women	Mean serum creatinine was 1.4±0.5 mg/dl in patients with IgA-GN and 1.8±0.6 mg/dl in patients with ADPKD	Self-report of cigarette smoking; calculated pack-years	ESKD (hemodialysis or kidney transplant)	The risk of ESKD in men with >5 pack-years, compared with <5 pack-years, was increased among those without ACE-inhibitor treatment (OR, 10.1; 95% CI, 2.3 to 4.5) but not those on ACE-inhibitor therapy (OR, 1.4; 95% CI, 0.3 to 7.1)
Chuahirun and Wesson 2002 (70), United States	N=33 Mean age: mean 46 yr With diabetes: 100% with type 2 Mean follow-up: 5.3 yr	Mean eGFR: 98 ml/min (Cockcroft–Gault)	Self-reported current cigarette smoker or nonsmoker	Slope of eGFR (ml/min over 5 years)	Greater eGFR decline among smokers compared with nonsmokers (−0.59 to −0.09 ml/min; P=0.009)
Yoshida *et al.* 2008 (71), Japan	N=485 Mean age: 41.5 yr With diabetes: not reported Follow-up: 2002–2007	CKD stage 1 and 2; mean eGFR: 86 ml/min per 1.73 m^2 (MDRD)	Self-reported current cigarette smoker or nonsmoker	Slope of eGFR (ml/min per 1.73 m^2 per year)	Smokers had greater eGFR decline than nonsmokers (−2.06 versus −1.58 ml/min per 1.73 m^2 per year; P=0.01)
Grams *et al.* 2012 (73), United States	N=1722 Mean age: 49 yr in no vascular disease group and 60 yr in vascular disease group With diabetes: 6% Follow-up: 17.6 yr	Mean eGFR: 38.8 ml/min per 1.73 m^2 (no vascular disease group);mean eGFR: 33.9 ml/min per 1.73 m^2 (vascular disease group)(CKD-EPI)	Self-reported current cigarette smoker or nonsmoker	Incident ESKD (dialysis or transplant)	Compared with nonsmokers, smokers were associated with higher risk of ESKD (aHR, 1.30; 95% CI, 1.09 to 1.55)
Tanaka *et al.* 2013 (103), Japan	N=416 Mean age: 64 yr With diabetes: 32% Median follow-up: 3.3 yr	Mean eGFR: 55 ml/min per 1.73 m^2 (Japanese-specific, creatinine-based equation)	Self-reported current cigarette smoker or nonsmoker	Composite of ESKD or doubling in creatinine	Compared with nonsmokers, smokers were not associated with ESKD (aHR, 1.25; 95% CI, 0.41 to 3.84)
Ozkok *et al.* 2013 (72), Turkey	N=323 with ADPKD Mean age: 53 yr With diabetes: not reported Mean follow-up: 8.3 yr	Mean eGFR: 60 ml/min per 1.73 m^2 (MDRD)	Self-reported current cigarette smoker or nonsmoker	Rapid progressor defined as >1 ml/min per year decline in eGFR	Smoking not associated with rapid progression (aHR, 0.78; 95% CI, 0.28 to 2.16)
Muntner *et al.* 2013 (9), United States	N=3093 Mean age: 72.2 yr With diabetes: 35% Median follow-up: 4 yr	Mean eGFR: 47 ml/min per 1.73 m^2 (CKD-EPI)	Self-reported cigarette use, and categorized as poor (current smoker), intermediate (former smoker, quit ≤12 mo), ideal (never smoker or quit >12 mo ago)	Incident ESKD	Compared with current smoking, nonsmoking was not associated with ESKD (aHR, 0.79; 95% CI, 0.50 to 1.23)

Table 7. (Continued)

Publication Details	Sample Description and Follow-Up	Kidney Function	Definition of Smoking	CKD Progression Measure(s)	Key Findings of Adjusted Analyses
Ricardo *et al.* 2015 (4), United States	*N*=3006 Mean age: 58 yr With diabetes: 45% Median follow-up: 4 yr	Mean eGFR: 43 ml/min per 1.73 m^2(cystatin C and Cr CRIC-specific equation)	Self-reported smoking (≥100 cigarettes in lifetime) and classified as current, past, or never smoker	Composite of 50% decrease in eGFR from baseline or incident ESKD	Compared with current smokers, past and never smokers had reduced risk of CKD progression (aHR, 0.79 [95% CI, 0.64 to 0.98] and 0.68 [95% CI, 0.55 to 0.84], respectively)
Staplin *et al.* 2016 (13), United States	*N*=6245 (part of RCT for simvastatin and ezetimibe versus placebo) Mean age: 61 yr With diabetes: 34% Median follow-up: 4.9 yr	CKD stages 2–5 (MDRD)	Self-reported current cigarette smoker, or previously been a regular smoker of cigarettes (former), or never smoker	Incident ESKD and composite of incident ESKD or doubling in creatinine	Compared with never smokers, former and current smokers had a similar rate of progression to ESKD and for the composite of ESKD or doubling in serum creatinine
Roehm *et al.* 2017 (79), United States	*N*=108 smokers and 108 nonsmokers with hypertension; all treated with ACE-inhibitorMean age: 50 yrDiabetes excluded Follow-up: 5 yr	Stage 2 CKD (eGFR 60–80 ml/min per 1.73 m^2) with spot UACR >200 mg/g(CKD-EPI using cystatin C)	Smokers consumed ≥10 cigarettes per day for ≥1 yr;all smokers underwent smoking-cessation intervention program	Change in eGFR	5-year eGFR was higher in quitters than in continued smokers (62.0±5.4 versus 52.9±5.6 ml/min per 1.73 m^2, $P<0.001$); this value was lower in quitters than in nonsmokers (64.7±5.6 ml/min per 1.73 m^2, $P=0.02$)
Bundy *et al.* 2018 (74), United States	*N*=3939 Mean age: 58 yr With diabetes: 48% Median follow-up: 5.5 yr	Mean eGFR: 44–51 ml/min per 1.73 m^2 (cystatin C and Cr CRIC-specific equation)	Self-reported smoking (≥100 cigarettes in lifetime) and classified as current, past, or never smoker; modeled as cumulative average exposure	Composite of 50% decrease in eGFR from baseline or incident ESKD	Compared with nonsmoking throughout follow-up, persistent smoking was not associated with CKD progression (aHR, 1.02; 95% CI, 0.86 to 1.21)
Lee *et al.* 2021 (75), South Korea	*N*=1951 Mean age: 54 yr With diabetes: 33% Mean follow-up: 3 yr	Mean eGFR: 53 ml/min per 1.73 m^2	Self-report smoking classified as nonsmoker, former, or current smoker; and calculated as pack-years	Composite 50% decrease in eGFR from baseline or incident ESKD	Compared with never smokers, former and current smokers were associated with increased risk of CKD progression (aHR, 1.54 [95% CI, 1.11 to 2.15] and 1.56 [95% CI, 1.09 to 2.22], respectively); compared with never smokers, smokers with ≥30 pack-years had increased risk of CKD progression (aHR, 1.94; 95% CI, 1.35 to 2.77)

ADPKD, autosomal dominant polycystic kidney disease; ACE, angiotensin-converting enzyme; OR, odds ratio; MDRD, modification of diet in renal disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aHR, adjusted hazard ratio; Cr, creatinine; CRIC, chronic renal insufficiency cohort; RCT, randomized controlled trial; UACR, urinary albumin-creatinine ratio.

Table 8. Summary of select epidemiologic studies of the association of alcohol use and CKD progression among people with established CKD

Publication Details	Sample Description and Follow-Up	Kidney Function	Definition of Alcohol	CKD Progression Measure(s)	Key Findings of Adjusted Analyses
Menon *et al.* 2010 (104), United States	*N*=618 Age: >65 yr With diabetes: 14% Mean follow-up: 5.6 yr	Reported as <60 ml/min per 1.73 m^2	Self-report alcohol consumption, categorized as none, former, current	Cystatin C–eGFR decline (>3 ml/min per 1.73 m^2 per year) dichotomous outcome	Compared with no alcohol consumption, former or current alcohol consumption was not associated with rapid kidney function decline (OR, 0.38 [95% CI, 0.14 to 1.01] and 0.73 [95% CI, 0.45 to 1.19], respectively)
Bundy *et al.* 2018 (74), United States	*N*=3939 Mean age: 58 yr With diabetes: 48% Median follow-up: 5.5 yr	Mean eGFR: 44–51 ml/min per 1.73 m^2 (cystatin C and Cr CRIC-specific equation)	Self-report alcohol consumption, categorized as drinkers if have one or more alcoholic beverage(s) per week; modeled as average persistent exposure over time	Composite of 50% decrease in eGFR from baseline or incident ESKD	Compared with nondrinking throughout follow-up, persistent alcohol drinking was not associated with CKD progression
Joo *et al.* 2020 (105), Republic of Korea	*N*=1883 in CKD cohort Mean age: 54 yr With diabetes: 33% Median follow-up: 2.95 yr	Mean eGFR 50 ml/min per 1.73 m^2 (CKD-EPI)	Self-report alcohol consumption, categorized as nondrinking, occasional drinking (<6 drinks/wk), regular drinking (≥6 drinks/wk); binge drinking ≥5 drinks per occasion	Composite of 50% decrease in eGFR from baseline or incident ESKD	Compared with nondrinkers, occasional and moderate drinking were not associated with CKD progression; compared with nondrinkers, occasional binge drinking, and regular binge drinking were associated with increased risk of CKD progression (aHR, 1.99 [95% CI, 1.33 to 2.98] and 2.19 [95% CI, 1.38 to 3.46], respectively)

OR, odds ratio; Cr, creatinine; CRIC, chronic renal insufficiency cohort; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; aHR, adjusted hazard ratio.

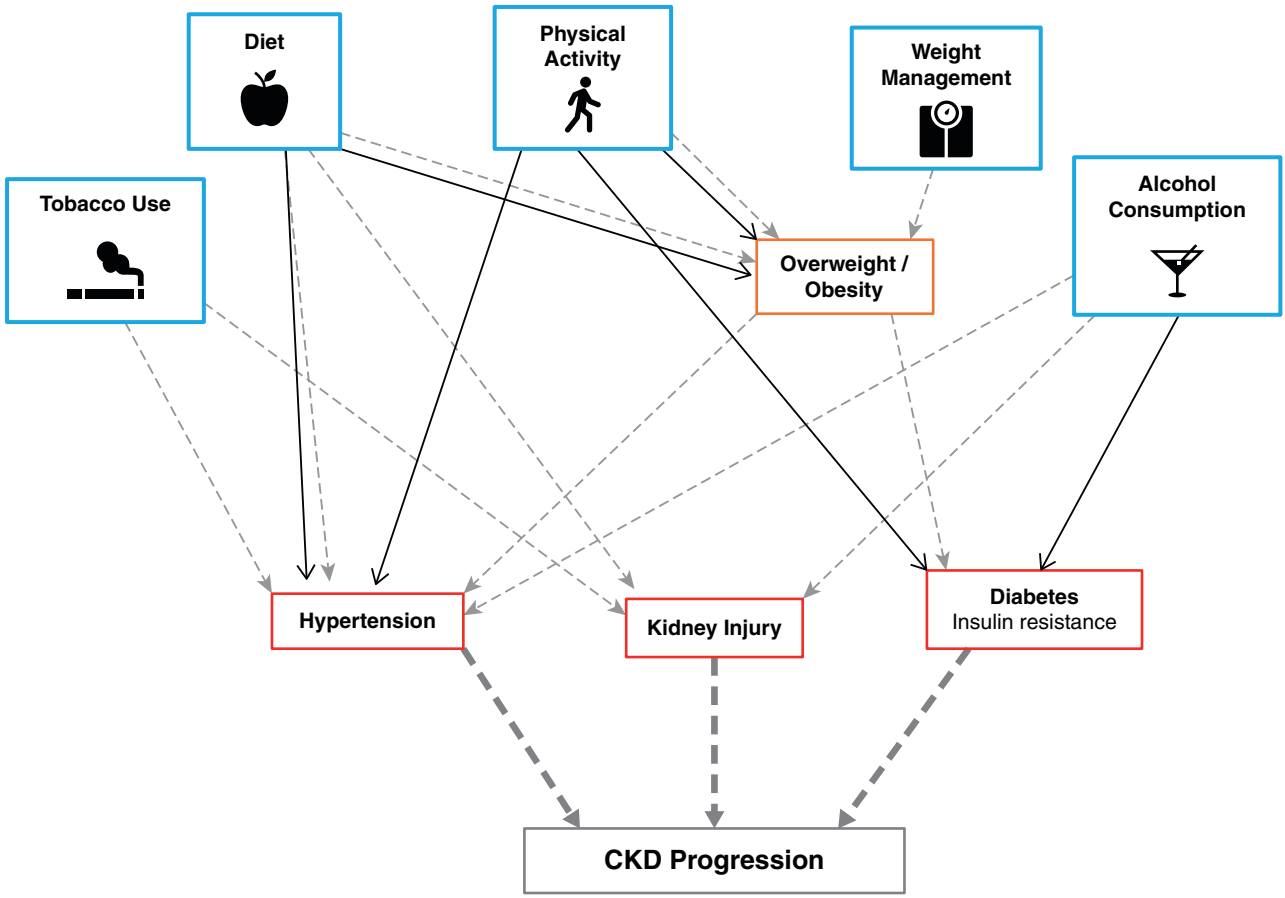

Figure 6. | Healthy lifestyle behaviors indirectly and/or directly influence cardiovascular health and CKD progression. Gray dashed arrows indicate a harmful effect, and a solid black line reflects a beneficial effect.

with established CKD (Table 8). According to these studies, only binge alcohol drinking was associated with increased risk of CKD progression, and other levels of drinking (*i.e.*, any, occasional, or moderate) were not associated with CKD progression. In the general population, reducing alcohol consumption among those who drink heavily has been demonstrated in RCTs to lower BP, but there are insufficient data on the risks or benefits of these interventions on BP in CKD populations, which precluded specific recommendations in the most recent KDIGO 2021 Guidelines for Blood Pressure and CKD (86).

Future Research Directions

Published KDOQI and KDIGO clinical practice guidelines that address lifestyle behaviors for the management of CKD in adults have identified research directions to address gaps in the evidence for delaying CKD progression (17,86,87). We summarize some of these recommendations here, including establishing the best methods to assess dietary intake and to support dietary change, such as nutritional education and dietary modification through shared decision making, behavior-modification techniques, and motivational interviewing. More research is needed to understand the role and potential benefits of using technology to assess dietary intake and to support behavior change. Clinical trials are needed to evaluate different strategies for sodium reduction, including identifying the amount of dietary sodium intake that is associated with improved outcomes among people with CKD. Further studies should compare the benefits of various intensity levels and types of physical activity, including the incorporation of resistance training in those with CKD. This research could also identify individual factors for patients with CKD that have the greatest benefit in terms of clinical outcomes, including BP control, that could inform personalized physical-activity recommendations. In terms of weight-management research, future efforts could determine the relationship of weight loss and renoprotection and compare the effect of various weight-loss strategies on clinical outcomes in CKD. Additional lifestyle behavior research should include the effect of behaviors in combination on CKD progression and other important clinical and patient-reported outcomes.

Lifestyle Behaviors in Practice

Despite lack of evidence of efficacy from large trials, maintaining a healthy lifestyle remains a cornerstone of CKD management because healthy lifestyle behaviors are largely modifiable and have been shown to improve cardiovascular health and BP control and are thought to indirectly or

directly affect CKD progression (Figure 6). It is reasonable that all adults with CKD receive counseling on the benefits of a healthy lifestyle, including diet, physical activity, smoking cessation, weight management, and moderation of alcohol intake, and it is equally important to address suboptimal lifestyle behavior adherence during routine clinic visits despite competing issues. Health-care providers can refer patients with CKD to medical nutrition therapy–trained dieticians who specialize in behavioral change plans that include exercise, nutrition, and stress control, and this service is covered by most health insurance plans (88). Lifestyle recommendations are of relevance in all countries, with limited to no public health costs, and have the potential to make far-reaching public health gains. The importance of lifestyle behaviors in CKD is underscored in the international CKD management guidelines with the following statement: "for the practicing clinician, ideally working with a team of health-care professionals, it is important to institute general lifestyle modifications practices in people with CKD so that they may gain the benefit of these in addition to more kidney-specific strategies" (89).

Disclosures

A.R. Chang reports having other interests in/relationships with National Kidney Foundation (grant support for NKF Patient Network); having consultancy agreements with Novartis (as consultant); receiving research funding from Novo Nordisk (investigator-sponsored study); receiving honoraria from Reata; and serving as a scientific advisor for, or member of, Reata and Relypsa. S.J. Schrauben reports receiving honoraria from Cowen and Company, LLC. The remaining author has nothing to disclose.

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Author Contributions

B.J. Apple, A.R. Chang, and S.J. Schrauben reviewed and edited the manuscript and were responsible for data curation; A.R. Chang and S.J. Schrauben were responsible for funding acquisition; A.R. Chang and S.J. Schrauben conceptualized the study and were responsible for formal analysis, investigation, and methodology; and S.J. Schrauben wrote the original draft.

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